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I, JANENE PEISKER, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Complete specification in connection with Application No. 2004200420 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 06 February 2004.

I further certify that pursuant to the provisions of Section 38(1) of the Patents Act 1990 Application No. 2004200420 is associated with Provisional Application No. 2003901100 and filed on 11 March 2003.

WITNESS my hand this
Fourth day of January 2006

JANENE PEISKER
MANAGER EXAMINATION SUPPORT
AND SALES

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COMPLETE SPECIFICATION
FOR A STANDARD PATENT
(ORIGINAL)

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Invention Title: "Inhibitor of cyclooxygenase"

Details of Associated Provisional Application Nos:

2003901100 filed 11 March 2003

The following statement is a full description of this invention, including the best method of performing it known to us:

D E S C R I P T I O N

INHIBITOR OF CYCLOOXYGENASE

TECHNICAL FIELD

This invention relates to pyrazole compounds and pharmaceutically acceptable salts thereof having pharmacological activity and to a process for their production.

Moreover, this invention relates to medicament or pharmaceutical composition comprising the above mentioned pyrazole compounds or pharmaceutically acceptable salts thereof as an active ingredient, to use of the compounds for the manufacture of a medicament and to analgesic agent.

BACKGROUND ART

Some pyrazole derivatives having anti-inflammatory and/or analgesic activities have been known, for example, WO 95/15316 and EP 0 418 845. However, most of example pyrazole compounds disclosed in these are substituted by two phenyl groups. On the other hand, the pyrazole compounds of this invention are substituted by at the least one 3-pyridyl group. And the compounds disclosed in WO 95/15316 selectively inhibit cyclooxygenase-II (COX-II) over cyclooxygenase-I (COX-I).

DISCLOSURE OF THE INVENTION

As a result of studies on the synthesis of pyrazole compounds and their pharmaceutical activity, the inventors of this invention have found that the pyrazole compounds of this invention have superior activity of inhibiting COX (especially, COX-I inhibiting activity). So, this invention relates to pyrazole compounds, which have pharmaceutical activity such as COX inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

Accordingly, one object of this invention is to provide the pyrazole compounds, which have a COX inhibiting activity.

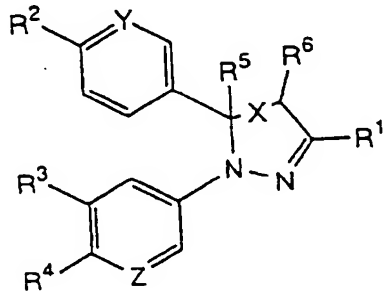
Another object of this invention is to provide a process for

production of the pyrazole compounds.

A further object of this invention is to provide medicament or pharmaceutical composition comprising the pyrazole compounds, as active ingredients.

Still further object of this invention is to provide a use of the pyrazole compounds for manufacturing a medicament for treating or preventing various diseases.

The pyrazole compounds of this invention can be represented by the following general formula (I):



(I)

wherein

R^1 is halogen, cyano, (lower alkyl)carbonyl, arylcarbonyl, lower alkyl, lower alkyl which is substituted with halogen, lower alkyl which is substituted with hydroxy, carboxy, (lower alkoxy)carbonyl, carbamoyl, N-(lower alkyl)carbamoyl, amino, or (lower alkoxy)carbonylamino;

R^2 is halogen, cyano, lower alkyl, lower alkoxy, carboxy, (lower alkoxy)carbonyl, or carbamoyl;

R^3 is hydrogen or lower alkyl;

R^4 is halogen, cyano, nitro, lower alkyl, lower alkoxy, amino, or heteroaryl containing nitrogen atom(s);

R^3 and R^4 may form 2,3-dihydrofuryl;

X is single or double bond between two carbon atoms;

R^5 is hydroxy and R^6 is hydrogen in case that X is single bond, or R^5 and R^6 do not exist in case that X is double bond;

Y is CH and Z is N, Y is N and Z is CH, or Y is N and Z is N;

or pharmaceutically acceptable salts thereof.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, and is preferably a fluorine atom or a chlorine atom, more preferably a chlorine atom.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

So, the "lower alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the like, and it is preferably C1-C4 alkyl, more preferably C1-C2 alkyl, most preferably methyl.

The "lower alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, and it is preferably C1-C4 alkoxy, more preferably C1-C2 alkoxy, most preferably methoxy.

The "(lower alkyl)carbonyl" means formyl and a monovalent group in which the above lower alkyl group substituted by carbonyl group (C1-C7 acyl), such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, pivaloyl, isovaleryl, hexanoyl, or the like, and it is preferably C1-C4 acyl, more preferably C1-C2 acyl, most preferably acetyl.

The "arylcarbonyl" means a monovalent group in which C6-C10 aryl group substituted by carbonyl group, such as benzoyl, naphthylcarbonyl, or the like, and it is preferably benzoyl.

The "lower alkyl which is substituted with halogen" means a monovalent group in which the above lower alkyl is subsutituted by 1 to 5 the above halogen atom(s), such as fluoromethyl,

chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like, and it is preferably C1-C4 alkyl which is substituted with halogen, more preferably C1-C2 alkyl which is substituted with halogen, more preferably C1-C2 alkyl which is substituted with fluorine atom(s), most preferably trifluoromethyl.

The "lower alkyl which is substituted with hydroxy" means a monovalent group in which the above lower alkyl is subsutituted by a -OH group, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-hydroxyisopropyl, 2-hydroxyisopropyl, hydroxybutyl, hydroxyisobutyl, hydroxy-tert-butyl, hydroxyhexyl, or the like, and it is preferably C1-C4 alkyl which is substituted with hydroxy.

The "(lower alkoxy)carbonyl" means a -CO_2-(lower alkyl) group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, or the like, and it is preferably (C1-C4 alkoxy)carbonyl, more preferably (C1-C2 alkoxy)carbonyl.

The "N-(lower alkyl)carbamoyl" means a carbamoyl group substituted by the above lower alkyl group on nitrogen atom, such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, tert-butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, or the like, and it is preferably (C1-C4 alkyl)carbamoyl, more preferably (C1-C2 alkyl)carbamoyl.

The "(lower alkoxy)carbonylamino" means a amino group substituted by the above (lower alkoxy)carbonyl group, such as methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, isopropoxycarbonylamino, butoxycarbonylamino, isobutoxycarbonylamino, tert-butoxycarbonylamino, pentoxycarbonylamino, hexoxycarbonylamino, or the like, and it is preferably (C1-C4 alkoxy)carbonyl.

The "heteroaryl containing nitrogen atom(s)" means 5- or 6-membered aromatic heterocyclic group containing 1 to 3 nitrogen atom(s). The "heteroaryl containing nitrogen atom(s)" may include 5-membered heteroaryl group such as pyrrolyl, imidazolyl, pyrazolyl; and 6-membered heteroaryl group such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or the like, and is preferably 5-membered heteroaryl group containing nitrogen atom(s), and it is preferably substituted on 1-position nitrogen atom.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

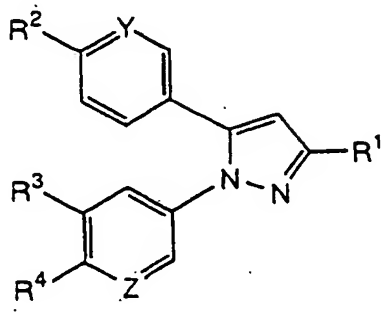
The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The pyrazole compounds of this invention can be converted to salt according to a conventional method. Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.),

a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

The pyrazole compound (I) may preferably include a compound of the formula (II):



(II)

wherein

R^1 is halogen, cyano, (lower alkyl)carbonyl, arylcarbonyl, lower alkyl, lower alkyl which is substituted with halogen, lower alkyl which is substituted with hydroxy, carboxy, (lower alkoxy)carbonyl, carbamoyl, N-(lower alkyl)carbamoyl, amino, or (lower alkoxy)carbonylamino;

R^2 is halogen, cyano, lower alkyl, lower alkoxy, carboxy, (lower alkoxy)carbonyl, or carbamoyl;

R^3 is hydrogen or lower alkyl;

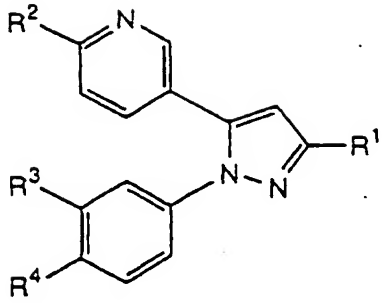
R^4 is halogen, cyano, nitro, lower alkyl, lower alkoxy, amino, or heteroaryl containing nitrogen atom(s);

R^3 and R^4 may form 2,3-dihydrofuryl;

Y is CH and Z is N, Y is N and Z is CH, or Y is N and Z is N;

or pharmaceutically acceptable salts thereof,

a compound of the formula (III):



(III)

wherein

R^1 is halogen, cyano, (lower alkyl)carbonyl, arylcarbonyl, lower alkyl, lower alkyl which is substituted with halogen, lower alkyl which is substituted with hydroxy, carboxy, (lower alkoxy)carbonyl, carbamoyl, N-(lower alkyl)carbamoyl, amino, or (lower alkoxy)carbonylamino;

R^2 is halogen, cyano, lower alkyl, lower alkoxy, carboxy, (lower alkoxy)carbonyl, or carbamoyl;

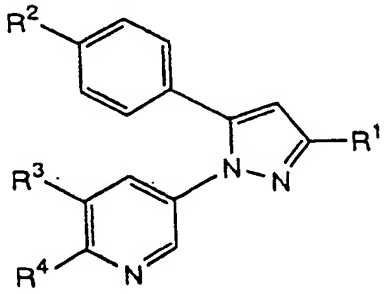
R^3 is hydrogen or lower alkyl;

R^4 is halogen, cyano, nitro, lower alkyl, lower alkoxy, amino, or heteroaryl containing nitrogen atom(s);

R^3 and R^4 may form 2,3-dihydrofuryl;

or pharmaceutically acceptable salts thereof,

a compound of the formula (IV):



(IV)

wherein

R^1 is halogen, cyano, (lower alkyl)carbonyl, arylcarbonyl, lower alkyl, lower alkyl which is substituted with halogen, lower alkyl which is substituted with hydroxy, carboxy, (lower alkoxy)carbonyl, carbamoyl, N-(lower alkyl)carbamoyl, amino, or (lower

alkoxy)carbonylamino;

R^2 is halogen, cyano, lower alkyl, lower alkoxy, carboxy, (lower alkoxy)carbonyl, or carbamoyl;

R^3 is hydrogen or lower alkyl;

R^4 is halogen, cyano, nitro, lower alkyl, lower alkoxy, amino, or heteroaryl containing nitrogen atom(s);

R^3 and R^4 may form 2,3-dihydrofuryl;

or pharmaceutically acceptable salts thereof, and

the above compound or pharmaceutically acceptable salts thereof, wherein

R^1 is halogen, cyano, arylcarbonyl, or lower alkyl which is substituted with halogen;

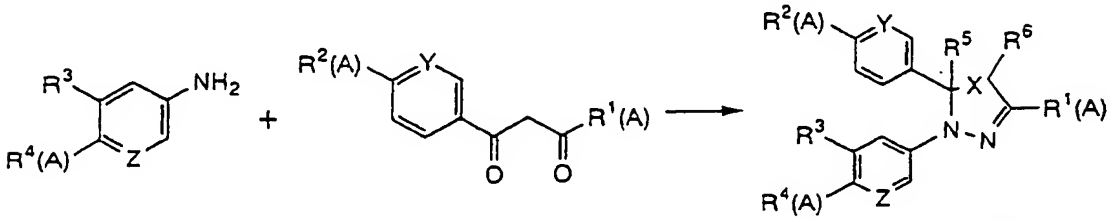
R^2 is cyano, lower alkyl, or lower alkoxy;

R^3 is hydrogen;

R^4 is lower alkoxy.

The compound of the formula (I) of the present invention can be prepared according to the following process.

Process A



(V) (VI) (IA)

In the above formulae, R^3, R^5, R^6, X, Y and Z represent the same meanings as defined above, $R^1(A)$ represents R^1 defined above except lower alkyl which is substituted with hydroxy, carboxy, carbamoyl, N-(lower alkyl)carbamoyl, amino, and (lower alkoxy)carbonylamino, $R^2(A)$ represents R^2 defined above except carboxy and carbamoyl, $R^4(A)$ represents R^4 defined above except amino.

Process A is the process for preparing the compound (IA), which corresponds to compound (I) in which R^1 to R^4 are not reactive groups.

This process is carried out by reacting compound (V) and compound (VI) under the acidic condition.

In this process, first, nitroso compound is formed by compound (V) and sodium nitrite ($NaNO_2$) under the acidic condition.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include water; alcohols such as methanol, ethanol, isopropanol; ethers such as diethyl ether, diisopropyl ether, tatrahydrofuran, dioxane; and mixed solvent of these.

The acid employable in this process for making acidic condition is not particularly limited so long as it is inactive in this reaction and may include hydrochloric acid, and the like.

The catalyst employable in this process is not particularly limited so long as it catalyze the reduction of nitroso compound from compound (V) and (VI) to hydrazine compound and may include tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$).

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from -10 °C to room temperature, preferably from 0 °C to 10 °C.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 5 min to 5 hr, preferably from 30 min to 1 hr.

The hydrazine compound formed by above reaction may be used in the next reaction without further purification in one pot. For example, after only evaporation of solvent, it can be used.

Then, to the hydrazine compound, compound (VI) is added for forming pyrazole ring or 3,4-dihydropyrazole ring.

This reaction is carried out under the acidic condition, for example, by using acetic acid as solvent.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 0 °C to 200 °C, preferably from room temperature to 80 °C.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 30 min to over night, preferably from 1 hr to 3 hr.

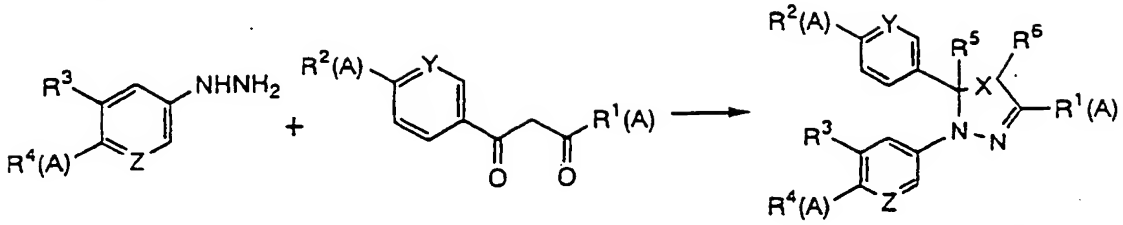
Whether the product of this process is pyrazole compound or 3,4-dihydropyrazole compound mainly depends on the reactivity of hydrazine compound. However, 3,4-dihydropyrazole compounds can be transformed into pyrazole compound by following Process C(2).

After the reaction, the desired compound (IA) is collected from the reaction mixture according to a conventional method. For example, the reaction mixture dilute with organic solvent immiscible with water such as ethyl acetate, it is washed with water, hydrochloric acid aq., aq. sodium bicarbonate, brine, etc, and this organic layer is dried over anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium hydrogencarbonate, etc. After evaporation of organic solvent, the desired compound is purified by the conventional method such as chromatography, recrystallization, etc.

Compound (IA) can also be synthesized according to the

following process.

Process B



(VII) (VI) (IA)

In the above formulae, $R^1(A)$, $R^2(A)$, R^3, $R^4(A)$, R^5, R^6, X, Y and Z represent the same meanings as defined above.

Process B the process for preparing the compound (IA), which corresponds to compound (I) in which R^1 to R^4 are not reactive groups.

In this process, compound (VII) is condensed to compound (VI) for synthesis of compound (IA).

This reaction is carried out under the acidic condition, for example, by using acetic acid as solvent.

Whether the product of this process is pyrazole compound or 3,4-dihydropyrazole compound mainly depends on the reactivity of hydrazine compound (VII). However, it is likely that in case that higher temperature is adapted, pyrazole compound (X is double bond) is formed, in case that lower temperature is adapted, 3,4-dihydropyrazole compound (X is single bond) is formed.

The reaction temperature varies depending on the starting material, the solvent, etc., but the higher temperature is usually from 50 °C to 200 °C, preferably from 50 °C to 120 °C and the lower temperature is usually from 10 °C to room temperature.

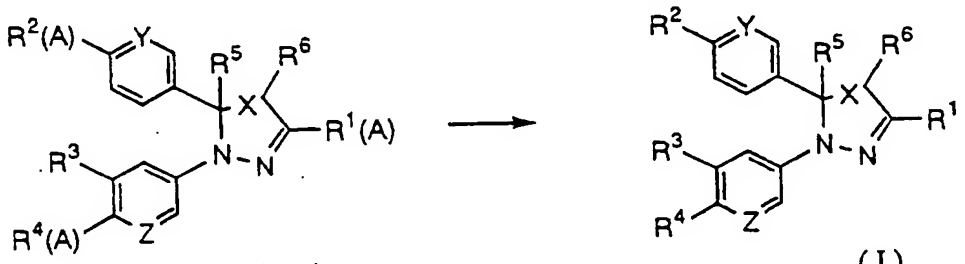
The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1 hr to 2 days, preferably from 2 hr to over night.

After the reaction, the desired compound (IA) is collected from the reaction mixture according to a conventional method. For example, the reaction mixture dilute with organic solvent immiscible with water such as ethyl acetate and water-like solvent such as hydrochloric acid aq., and then the organic layer is separated and washed with water, sodium bicarbonate, brine, etc,

and this organic layer is dried over anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium hydrogencarbonate, etc. After evaporation of organic solvent, the desired compound is purified by the conventional method such as chromatography, recrystallization, etc.

Compound (IA) can be transformed into compound (I) by following process.

Process C



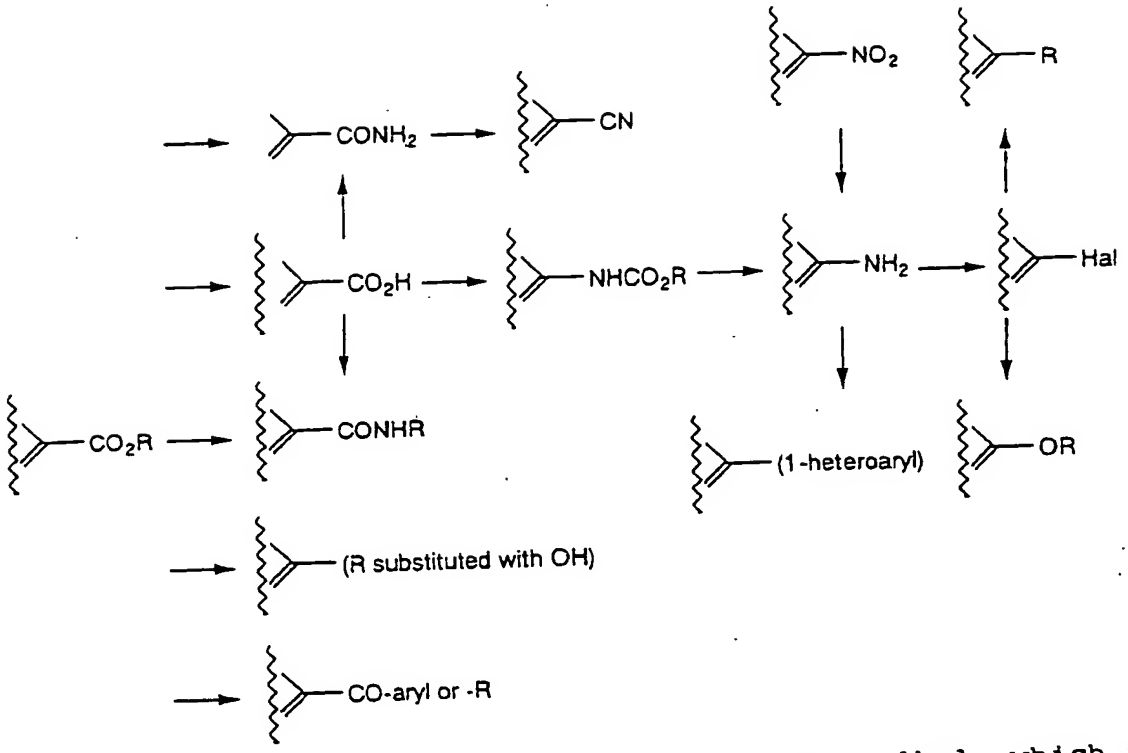
(IA) (I)

In the above formulae, $R^1(A)$, $R^2(A)$, $R^4(A)$, $R^1 \sim R^6$, X, Y and Z represent the same meanings as defined above.

Process C the process for preparing the compound (I) from compound (IA).

This process is carried out by functional group trans formation, which is obvious to the person skilled in the organic chemistry. For example, such reactions are illustrated as following.

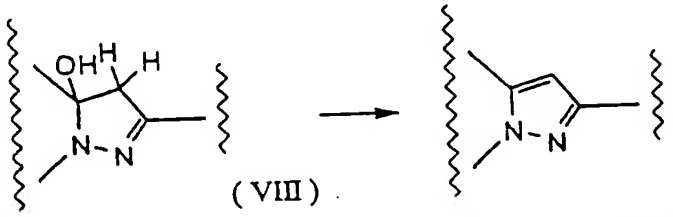
Process C(1)



In the above formulae, R represents lower alkyl, which is not specified.

And pyrazole ring can be formed by following reaction.

Process C(2)



(VIII) (IX)

In the above, compound (VIII) is the compound (I) or (IA) of which X is single bond (R^5 is hydroxy and R^6 is hydrogen), and compound (IX) is the compound (I) or (IA) of which X is double bond.

This reaction is carried out by ordinal dehydrate reaction, which is, for example, heat reaction under acidic condition.

The solvent employable in this process is not particularly limited, but acid such as acetic acid, sulfuric acid or the like may be used as solvent.

The reaction temperature varies depending on the starting

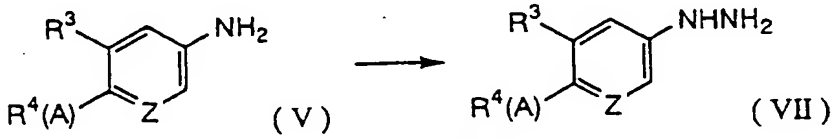
material, the solvent, etc., but it is usually from 50 °C to 200 °C, preferably from 80 °C to 150 °C.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 30 min to 5 hr, preferably from 1 hr to 3 hr.

This dehydrate reaction may be carried out at the same tame that above functional group trans formation (Process C(1)) is carried out.

Compound (VII) can be synthesized from compound (V) by following process other than purchase.

Process D



In the above formulae, R^3, $R^4(A)$ and Z represent the same meanings as defined above.

Process D the process for preparing the compound (VII), which is the starting material of Process B.

In this process, first, nitroso compound is derived from compound (V) and sodium nitrite ($NaNO_2$), and then the nitroso compound is reduced to hydrazine compound with catalyst under the acidic condition.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include water; alcohols such as methanol, ethanol, isopropanol; ethers such as diethyl ether, diisopropyl ether, tatrahydrofuran, dioxane; and mixed solvent of these.

The acid employable in this process for making acidic condition is not particularly limited so long as it is inactive in this reaction and may include hydrochloric acid, and the like.

The catalyst employable in this process is not particularly limited so long as it catalyze the reduction of nitroso compound from compound (V) and (VI) and may include tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$).

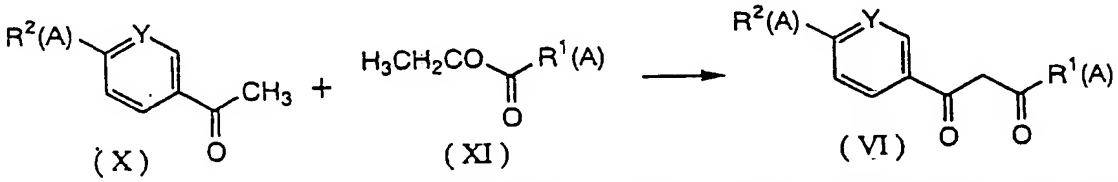
The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from -10 °C to room temperature, preferably from 0 °C to 10 °C.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 5 min to 5 hr, preferably from 30 min to 1 hr.

After the reaction, the desired compound (VII) is collected from the reaction mixture according to a conventional method. For example, the solvent is evaporated, and if necessary, the desired compound is purified by the conventional method such as chromatography, recrystallization, etc. But, compound (VII) may be used in next reaction step without purification.

Compound (VI) can be synthesized from compound (X) and (XI) by following process other than purchase.

Process E



In the above formulae, $R^1(A)$, $R^2(A)$ and Y represent the same meanings as defined above.

Process E is the process for preparing the compound (X), which is the starting material of Process A and B.

In this process, first, carboanion of compound (V) is derived by strong base, and then the carboanion attacks compound (XI) and EtO^- group is eliminated.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as methanol, ethanol, isopropanol; amides such as N,N-dimethylformamide, dimethylacetamide, hexamethylphosphoric triamide; and so on.

The strong base employable in this process is not particularly limited so long as it can abstract αH from compound (X) and may include sodium methoxide, sodium ethoxide, sodium hydride, and so on.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from -20 °C to room temperature.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 30 min to 5 hr, preferably from 1 hr to 2 hr.

After the reaction, the reaction mixture is diluted by water and hydrochloric acid aq., etc to decompose excess strong base. The desired compound (VI) is collected from the reaction mixture according to a conventional method. For example, the desired compound is filtered and dried, or the reaction mixture is dilute with organic solvent immiscible with water such as ethyl, and then the organic layer is separated and washed with water, sodium bicarbonate, brine, etc, and this organic layer is dried over anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium hydrogencarbonate, etc. After evaporation of organic solvent, the desired compound is purified by the conventional method such as chromatography, recrystallization, etc.

Above processes (Process A ~ E), all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method.

Starting materials of above each process may be purchased if they are commercial, synthesized according to above processes (Process D, E) or other general methods from commercial compounds, because compound (V) ~ (VII), (X) and (XI) as starting compound for synthesis of compound (I) have comparatively simple structure.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may

be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

THE BEST MODE FOR CARRYING OUT THE INVENTION

The patents, patent applications and publications cited herein are incorporated by reference.

The following Examples and Preparations are given only for the purpose of illustrating the present invention in more detail.

Example 1

5-(4-Cyanophenyl)-3-difluoromethyl-1-(6-methoxy-3-pyridyl)-1 H-pyrazole

To a solution of 0.62 g (5.0 mmol) 5-amino-2-methoxy-pyridine in 10 ml 1 N hydrochloric acid at 5°C, was added 414 mg (6.0 mmol) sodium nitrite in 3 ml water, stirred 30 min. at 5°C, then added 4.06 g (18 mmol) tin (II) chloride dihydrate, stirred 30 min. at 5oC, evaporated. Added 0.89 g (4.0 mmol) 4-(4,4-difluoro-3-oxobutanoyl)benzonitrile and 10 ml acetic acid, heated at 100°C for one hour; cooled, diluted with ethyl acetate, washed with 3 N hydrochloric acid (three times), sat. aq. sodium bicarbonate (three times), brine, dried (magnesium sulfate), filtered, evaporated.

Purification by column chromatography (silica gel,

toluene/hexane) followed by recrystallization from diethyl ether/hexane gave 415 mg of desired compound as white crystals (31.8%).

MP : 83-84°C.

MS : 327 (M + 1).

NMR (DMSO, δ) : 3.88(3H, s), 6.92(1H, d, J=8.8), 7.15 (1H, t, J=54), 7.15(1H, s), 7.47-7.53(2H, m), 7.75(1H, dd, J=8.8, 2.8), 7.84-7.92(2H, m), 8.18(1H, d, J=2.2).

Example 2

5-(4-Cyanophenyl)-1-(6-methoxy-3-pyridyl)-3-trifluoromethyl-1H-pyrazole hydrochloride

Reaction was carried out in a manner similar to Example 1 using 5-amino-2-methoxy-pyridine and 4-(4,4,4-trifluoro-3-oxobutanoyl)benzonitrile to give 340 mg of desired compound as white crystals (22.3%).

MP : 140-144°C.

MS : 345 (free base + 1)

NMR (DMSO, δ) : 3.89 (3H, s), 6.94 (1H, d, J=8.8), 7.39 (1H, s), 7.49-7.56 (2H, m), 7.79 (1H, dd, J=8.8, 2.6), 7.86-7.93 (2H, m), 8.22 (1H, d, J=2.6).

Example 3

5-(4-Cyanophenyl)-3-(ethoxylcarbonyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 1 using 5-amino-2-methoxy-pyridine and 4-(3-ethoxycarbonyl-3-oxopropanoyl)benzonitrile to give 1.33 g of desired compound as yellow crystals (23.9%).

MP : 130-131°C.

349 (M + 1).

NMR (DMSO, δ) : 1.32 (3H, t, J=7.1), 3.89 (3H, s), 4.35 (2H, q, J=7.1), 6.94 (1H, d, J=8.9), 7.31 (1H, s), 7.47-7.53 (2H, m), 7.77 (1H, dd, J=8.9, 2.4), 7.84-7.90 (2H, m), 8.18 (1H, d, J=2.4).

Example 4

3-Carbamoyl-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

A solution of 0.65 g (1.86 mmol) 5-(4-cyanophenyl)-3-(ethoxylcarbonyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 3, 5 ml formamide and 100 mg sodium ethoxide was heated at 100°C for three hours, cooled, diluted with ethyl acetate, washed with water (three times), brine, dried (magnesium sulfate), filtered, evaporated to give 0.42 g of desired compound as a white solid (70.7%).

MS : 342 (M + Na).

NMR (DMSO, δ) : 3.88 (3H, s), 6.93 (1H, d, J=8.8), 7.16 (1H, s), 7.42 (1H, s), 7.49 (2H, d, J=8.4), 7.74 (1H, s), 7.75 (1H, dd, J=8.8,.2.6), 7.87 (2H, d, J=8.4), 8.20 (1H, d, J=2.6).

Example 5

3-Cyano-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

A solution of 0.70 ml phosphorus oxychloride and 5 ml dimethylformamide was stirred at 5°C under nitrogen for 30 min., then was added 0.39 g (1.22 mmol) 3-carbamoyl-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 4, stirred at 5°C, one hour. Poured into ice/water, added ethyl acetate, then solid potassium carbonate until neutral. Separated, washed with sat. aq. sodium bicarbonate, brine, dried (magnesium sulfate), filtered, evaporated. Recrystallized from ethyl acetate to give 172 mg

of desired compound as white crystals (46.8%).

MP : 158-159°C.

MS : 324 (M + Na).

NMR (DMSO, δ) : 3.89 (3H, s), 6.94 (1H, d, J=8.9), 7.45-7.54 (2H, m), 7.58 (1H, s), 7.77 (1H, dd, J=8.9, 2.8), 7.86-7.95 (2H, m), 8.22 (1H, d, J=2.8).

Example 6

3-Carboxy-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 20 using 5-(4-cyanophenyl)-3-(ethoxylcarbonyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 3 to give 1.45 g of desired compound as an off white solid. (98.4%)

MS : 343 (M + Na).

NMR (DMSO, δ) : 3.89(3H, s), 6.93(1H, d, J=9.0), 7.24(1H, s), 7.46-7.53(2H, m), 7.75(1H, dd, J=9.0, 2.4), 7.88-7.96(2H, m), 8.18(1H, d, J=2.4).

Example 7

3-(tert-Butoxycarbonylamino)-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 21 using 3-carboxy-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 6 to give 0.13 g of desired compound as green crystals (13.3%).

MS : 390 (M - 1).

NMR (DMSO, δ) : 1.47(9H, s), 3.86(3H, s), 6.82(1H, s), 6.88(1H,

d, J=9.1), 7.45(2H, d, J=8.3), 7.62(1H, dd, J=9.1, 2.6), 7.84(2H, d, J=8.3), 8.04(1H, d, J=2.6), 9.92(1H, s).

Example 8

3-Amino-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 22 using 3-(tert-butoxycarbonylamino)-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 7 to give 0.32 g of desired compound as white crystals (99.8%).

MS : 292 (M + 1).

NMR (DMSO, δ) : 3.84(3H, s), 5.08(2H, s), 5.99(1H, s), 6.83(1H, d, J=8.7), 7.37-7.44(2H, m), 7.54(1H, dd, J=8.7, 2.8), 7.79-7.85(2H, m), 7.94(1H, d, J=2.8).

Example 9

3-Chloro-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 23 using 3-amino-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 8 to give 156 mg of desired compound as white crystals (45.6%).

MP : 121-122°C.

MS : 333 (M + Na).

NMR (DMSO, δ) : 3.88(3H, s), 6.91(1H, d, J=8.6), 7.00(1H, s), 7.44-7.50(2H, m), 7.72(1H, dd, J=8.6, 2.5), 7.84-7.90(2H, m), 8.14(1H, d, J=2.5).

Example 10

5-(4-Cyanophenyl)-3-(N-ethylcarbamoyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 24 using 3-carboxy-5-(4-cyanophenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 6 to give 55 mg of desired compound as white crystals (15.8%).

MP : 169-170°C.

MS : 370 (M + Na).

NMR (DMSO, δ) : 1.10(3H, t, J=7.1), 3.20-3.29(2H, obscured by solvent), 3.88(3H, s), 6.93(1H, d, J=8.8), 7.16(1H, s), 7.49(2H, d, J=8.4), 7.77(1H, dd, J=8.8, 2.5), 7.86(2H, d, J=8.4), 8.20(1H, d, J=2.5), 8.38(1H, t, J=5.8).

Example 11

3-Difluoromethyl-5-(4-ethoxylcarbonylphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 1 using 5-amino-2-methoxy-pyridine and ethyl 4-(4,4-difluoro-3-oxobutanoyl)benzoate to give 0.51 g of desired compound as a yellow solid (17.1%).

MS : 396 (M + Na).

NMR (DMSO, δ) : 1.27(3H, t, J=7.1), 3.88(3H, s), 4.31(2H, q, J=7.1), 6.91(1H, d, J=8.8), 7.15(1H, t, J=54.2), 7.40-7.49(2H, m), 7.73(1H, dd, J=8.8, 2.7), 7.89-7.98(2H, m), 8.15(1H, d, J=2.7).

Example 12

5-(4-Carboxyphenyl)-3-difluoromethyl-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 20

using
3-difluoromethyl-5-(4-ethoxylcarbonylphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole to give 0.37 g of desired compound as a yellow solid. (81.8%)

MS : 344 (M - 1).
NMR (DMSO, δ) : 3.88(3H, s), 6.91(1H, d, J=8.8), 7.08(1H, s), 7.14(1H, t, J=54.3), 7.42(2H, dd, J=8.8, 2.4), 7.92(2H, d, J=8.3), 8.15(1H, d, J=2.4), 13.1(1H, br s).

Example 13
5-(4-carbamoylphenyl)-3-difluoromethyl-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 24 using
5-(4-carboxyphenyl)-3-difluoromethyl-1-(6-methoxy-3-pyridyl)-1H-pyrazole to give 238 mg of desired compound as white crystals (66.5%).

MP : 185-186°C.
MS : 367 (M + Na).
NMR (DMSO, δ) : 3.88(3H, s), 6.92(1H, d, J=8.5), 7.05(1H, s), 7.13(1H, t, J=54.4), 7.38(2H, d, J=8.4), 7.44(1H, s), 7.73(1H, dd, J=8.6, 2.6), 7.85(2H, d, J=8.3), 8.01(1H, br s), 8.15(1H, d, J=2.4).

Example 14
1-(6-Methoxy-3-pyridyl)-5-(4-methylphenyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 1 using 5-amino-2-methoxy-pyridine and
4-methyl-1-(4,4,4-trifluoro-3-oxobutanoyl)benzene to give 0.25 g of desired compound as a clear colorless oil (15.0%).

MS : 356 (M + Na).

NMR (DMSO, δ) : 2.30(3H, s), 3.88(3H, s), 6.91(1H, d, J=8.8), 7.15(1H, s), 7.21(4H, s), 7.75(1H, dd, J=8.8, 2.8), 8.17(1H, d, J=2.8).

Example 15

3-Difluoromethyl-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 1 using 5-amino-2-methoxy-pyridine and 4-methyl-1-(4,4-difluoro-3-oxobutanoyl)benzene to give 273 mg of desired compound as white crystals (21.6%).

MP : 85-87°C.

MS : 338 (M + Na).

NMR (DMSO, δ) : 2.30(3H, s), 3.87(3H, s), 6.90(1H, d, J=8.6), 6.91(1H, s), 7.10(1H, t, J=54.4), 7.19(4H, s), 7.70(1H, dd, J=8.6, 2.7), 8.12(1H, d, J=2.7).

Example 16

3-Ethoxylcarbonyl-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 1 using 5-amino-2-methoxy-pyridine and 1-(3-ethoxylcarbonyl-3-oxopropanoyl)-4-methylbenzene to give 2.62 g of desired compound as a green liquid (48.5%).

MS : 338 (M + 1).

NMR (DMSO, δ) : 1.32(3H, t, J=7.1), 2.30(3H, s), 3.88(3H, s), 4.33(2H, q, J=7.1), 6.91(1H, d, J=8.9), 7.08(1H, s), 7.18 (4H, s), 7.72(1H, dd, J=8.9, 2.5), 8.14(1H, d, J=2.5).

Example 17

3-(1-Hydroxy-1-methylethyl)-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole

To a solution of 0.33 g (1.0 mmol) 3-ethoxylcarbonyl-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole obtained by Example 16 in 2 ml tetrahydrofuran at 5°C under nitrogen was added 6 ml 1 N methyl magnesium bromide in tetrahydrofuran all at once. After 30 min. quenched with isopropanol, diluted with ethyl acetate, water, acidified with aq. hydrochloric acid, separated, washed with brine, dried (magnesium sulfate), filtered, evaporated to give 0.29 g of desired compound as a green oil (89.7%).

MS : 346 (M + Na).

NMR (DMSO, δ) : 1.49(6H, s), 2.30(3H, s), 3.85(3H, s), 5.02(1H, s), 6.56(1H, s), 6.86(1H, d, J=8.9), 7.09-7.22(4H, m), 7.61(1H, dd, J=8.9, 2.6), 8.00(1H, d, J=2.6).

Example 18

3-Carbamoyl-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 4 using 3-ethoxylcarbonyl-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole obtained by Example 16 to give 0.53 g of desired compound as a white solid (99.9%).

MS : 309 (M + 1).

NMR (DMSO, δ) : 2.30(3H, s), 3.87(3H, s), 6.90(1H, d, J=8.8), 6.94(1H, s), 7.18(4H, s), 7.36(1H, s), 7.65(1H, s), 7.71(1H, dd, J=8.8, 2.2), 8.15(1H, d, J=2.2).

Example 19

3-Cyano-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 5 using 3-carbamoyl-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole obtained by Example 18 to give 200 mg of desired compound as white crystals (42.5%).

MP : 99-101°C.
MS : 291 (M + 1).
NMR (DMSO, δ) : 2.30(3H, s), 3.88(3H, s), 6.92(1H, d, J=8.8), 7.13-7.25(4H, m), 7.38(1H, s), 7.74(1H, dd, J=8.8, 2.3), 8.19(1H, d, J=2.3).

Example 20
3-Carboxy-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole

A solution of 1.43 g (4.23 mmol) 3-ethoxylcarbonyl-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole obtained by Example 16, 20 ml methanol and 25 ml 1 N sodium hydroxide was heated at reflux for one hour, cooled, diluted with water, added hydrochloric acid until strongly acidic, allowed to stand one hour, collected by filtration, washed with water, air dried to give 1.13 g of desired compound as a yellow solid (86.4%).

MS : 332 (M + Na).
NMR (DMSO, δ) : 2.30(3H, s), 3.88(3H, s), 6.91(1H, d, J=8.8), 7.02(1H, s), 7.21(4H, s), 7.71(1H, dd, J=8.8, 2.5), 8.13(1H, d, J=2.5), 12.98(1H, s).

Example 21
3-(tert-Butoxycarbonylamino)-1-(6-methoxy-3-pyridyl)-5-(4-me

thylphenyl)-1H-pyrazole

A solution of 773 mg (2.5 mmol) 3-carboxy-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole obtained by Example 20, 5 ml tert-butanol, 0.81 ml (3.75 mmol, 1.5 eq.) diphenylphosphoryl azide, and 0.52 ml (3.75 mmol, 1.5 eq.) triethylamine was heated at reflux overnight (22 hours). Cooled, evaporated, diluted with ethyl acetate, washed with water, dilute hydrochloric acid (three times), sat. aq. sodium bicarbonate (three times), brine, dried (magnesium sulfate), filtered, evaporated. Purification by column chromatography over silica gel (toluene/ethyl acetate) followed by recrystallization from ethyl acetate gave 0.63 g of desired compound as white crystals (66.2%).

MP : 169-170°C.

MS : 281 (M - BOC + 1), 325 (M - tBu + 1).

NMR (DMSO, δ) : 1.47(9H, s), 2.30(3H, s), 3.88(3H, s), 6.63(1H, s), 6.85(1H, d, J=8.8), 7.10-7.26(4H, m), 7.58(1H, dd, J=8.8, 2.7), 7.99(1H, d, J=2.7), 9.82(1H, s).

Example 22

3-Amino-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole

To a solution of 0.76 (2.00 mmol) 3-(tert-butoxycarbonylamino)-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole obtained by Example 21 in ethyl acetate was added 20 ml 4 N hydrochloric acid in ethyl acetate at room temperature, stirred one hour. Poured into water/ethyl acetate, neutralized with potassium carbonate, separated, washed with brine, dried (magnesium sulfate), filtered, evaporated to give 0.49 g of desired compound as a yellow oil (87.4%).

MS : 281 (M + 1).

NMR (DMSO, δ) : 2.29(3H, s), 3.87(3H, s), 4.95(2H, s), 5.81(1H, s), 6.79(1H, d, J=8.8), 7.06-7.19(4H, m), 7.50(1H, dd, J=8.8, 2.7), 7.89(1H, d, J=2.7).

Example 23

3-Chloro-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole

A mixture of 0.49 g (1.75 mmol) 3-amino-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole obtained by Example 22, 0.54 g (4.0 mmol) copper (II) chloride, 0.42 g (10 mmol) lithium chloride, and 12 ml acetonitrile was stirred for 5 min. at room temperature. Added 0.40 ml (3.0 mmol) isoamyl nitrite at room temperature, stirred for one hour, then one hour at reflux, cooled, added 1N hydrochloric acid and ethyl acetate, separated, washed with 1N hydrochloric acid, brine, dried (magnesium sulfate), filtered, evaporated. Purified by silica gel column chromatography (toluene/ethyl acetate) followed by recrystallization from ethyl acetate/hexane to give 234 mg of desired compound as white crystals (44.6%).

MP : 100-102°C.

MS : 300 (M + 1).

NMR (DMSO, δ) : 2.30(3H, s), 3.86(3H, s), 6.77(1H, s), 6.88(1H, d, J=9.1), 7.11-7.23(4H, m), 7.66(1H, dd, J=9.1, 2.4), 8.09(1H, d, J=2.4).

Example 24

3-(N-Ethylcarbamoyl)-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole

To a solution of 309 mg (1.0 mmol) 3-carboxy-1-(6-methoxy-3-pyridyl)-5-(4-methylphenyl)-1H-pyrazole obtained by Example 20 in 5 ml dichloromethane was added 0.20 ml oxalyl chloride. Added one drop dimethylformamide, then

stirred for one hour at room temperature. Evaporated, added 5 ml toluene and evaporated again. Added 5 ml dichloromethane, cooled to 5°C, added 245 mg (3.0 mmol) ethyl amine hydrochloride followed by 0.42 ml (3.0 mmol) triethylamine. Removed the cold bath and stirred at room temperature overnight. Diluted with ethyl acetate, water, acidified with 3N hydrochloric acid, separated. Washed with aq. hydrochloric acid (twice), dilute aq. sodium hydroxide (three times), brine, dried (magnesium sulfate), filtered, evaporated. Purification on silica gel (toluene/ethyl acetate) followed by recrystallization from diethyl ether gave 238 mg desired compound as white crystals (70.8%).

MP : 136-137°C.

MS : 359 (M + Na).

NMR (DMSO, δ) : 1.10(3H, t, J=7.1), 2.30(3H, s), 3.15-3.23(2H, obscured by solvent), 3.88(3H, s), 6.91(1H, d, J=8.7), 6.94(1H, s), 7.18(4H, s), 7.73(1H, dd, J=8.8, 2.5), 8.15(1H, d, J=2.5), 8.31(1H, t, J=5.7).

Example 25

1-(6-Chloro-3-pyridyl)-5-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole

A solution of 5-amino-2-chloropyridine (7.7g) in acetic acid (80ml) was stirred under ice-water bath. $NaNO_2$ (3.67g) was added to above solution at the same temperature. Conc. hydrochloric acid (20ml) was added to the resulting mixture and stirred for 30min at the same temperature. $SnCl_2$ (24.7g) was added at same temperature and stirred at ambient temperature. 4-(4,4,4-Trifluoro-3-oxobutanoyl)chlorobenzene (6.03g) was added to the reaction mixture. The reaction mixture was stirred for additional 1hr at 110℃. The resulting mixture was evaporated. To the residue was added 6N NaOH-etyl acetate and then filtrate on celite. The organic layer was separated and dried over

magnesium sulfate and evaporated. The residue was purified by column chromatography (Silica/Toluene) ethyl acetate 10% to afford 4.1g of desired compound (37.1%).

MP : 55-56℃.

MS : 354(M + 1), 355(M + 3)

NMR($CDCl_3$, δ) : 3.83(3H, s), 6.72(1H, s), 6.74(1H, d, J=8Hz), 6.90-7.20(4H, m), 7.56(1H, d, J=8,2Hz), 8.10(1H, d, J=2Hz).

Example 26

1-(6-Methoxy-3-pyridyl)-5-(4-methoxyphenyl)-3-trifluoromethy 1-1H-pyrazole

A mixture 1-(6-chloro-3-pyridyl)-5-(4-methoxyphenyl)-3-trifluoromethyl -1H-pyrazole (1.0g) obtained by Example 25 and sodium methoxide (420mg) in methanol (5ml) was stirred for 1hr at 80℃. The reaction mixture was extracted with ethyl acetate - water. The organic layer was dried with magnesium sulfate and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate to afford 620mg of desired compound (62.8%).

MP : 71-75℃.

MS : 350(M + 1).

NMR($CDCl_3$, δ) : 3.81(3H, s), 3.94(3H, s), 6.69(1H, s), 6.80-7.20(4H, m), 7.35(1H, d, J=8Hz), 7.67(1H, d, J=8.2Hz), 8.32(1H, d, J=2Hz).

Example 27

3-Ethoxycarbonyl-5-(4-methoxyphenyl)-1-(6-methoxy-3-pyridyl) -1H-pyrazole

A mixture of 4-(3-ethoxycarbonyl-3-oxopropanoyl)methoxybenzene (4.0g), 5-hydrazino-2-methoxypyridine hydrochloride obtained by Preparation 1 (3.51g) in acetic acid (20ml) was stirred at 60°C

for 2.0 hours. After cooling, the reaction mixture was diluted with ethyl acetate and 1N hydrochloric acid. An organic layer was separated, washed with sat. sodium bicarbonate (twice), water, and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (100ml, hexane/ethyl acetate) to give 2.53g of desired compound (44.8%).

MP : 90-91°C.
MS : 354(M + 1).
IR (KBr) : 1724.05, 1610.27, 1498.42, 1390.42, 1292.07, 1253.50, 1228.43, 1024.02.
NMR ($CDCl_3$, δ) : 1.423(3H, t, J=7.10 Hz), 3.809(3H, s), 3.940(3H, s), 4.452(2H, q, J=7.10 Hz), 6.733(1H, d, J=8.83 Hz), 6.851(2H, d, J=8.93 Hz), 6.980(1H, s), 7.142(2H, d, J=8.93 Hz), 7.573(1H, dd, J=8.83and2.74 Hz), 8.114(1H, d, J=2.74 Hz).

Example 28
3-Difluoromethyl-5-(4-methoxyphenyl)-1-(6-methoxy-3-pyridyl) -1H-pyrazole

Reaction was carried out in a manner similar to Example 27 using 5-hydrazino-2-methoxypyridine hydrochloride and 1-methoxy-4-(4,4-difluoro-3-oxobutanoyl)benzene to give 727 mg of desired compound (54%).

MS : 354(M + Na).
IR (KBr) : 1610.27, 1498.42, 1461.78, 1390.42, 1292.07, 1253.50, 1172.51, 1083.80, 1027.87, 833.098, 673.035.
NMR ($CDCl_3$, δ) : 3.812(3H, s), 3.942(3H, s), 6.671(3H, s), 6.738(1H, d, J=8.87 Hz), 6.755(1H, t, J=55.0 Hz -gemF2), 6.858(2H, d, J=8.71 Hz), 7.153(2H, d, J=8.71 Hz), 7.528(1H, dd, J=8.87, 2.42 Hz), 7.591(1H, d, J=2.42 Hz).

Example 29

3-Benzoyl-5-(4-methoxyphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

To a solution of 3-ethoxycarbonyl-1-(6-methoxy-3-pyridyl)-5-(4-methoxyphenyl)-1H-pyrazole obtained by Example 27 (300mg) and N,O-dimethylhydroxylamine hydrochloride (104mg) in tetrahydrofuran (10ml) was added dropwise phenyl magnesium bromide (1M, 3.4ml) under ice cooling. After stirring for 1 hr, the reaction mixture was poured onto ethyl acetate and 1N hydrochloric acid. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with 1N hydrochloric acid, sat. aq. sodium bicarbonate, water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml, ethyl acetate/hexane) and recrystalized from isopropylether to give 162mg of desired compound (49.5%). The filtrate was evaporated and recrystalized from isopropylether to give 30mg of second crystal (9.2%).

MP : 132-134°C.
MS : 386(M + 1).
IR (KBr) : 1648.84, 1608.34, 1498.42, 1450.21, 1388.50, 1290.14, 1247.72, 1180.22, 1024.02, 896.74, 831.17, 730.89, 694.25.
NMR ($CDCl_3$, δ) : 3.823(3H, s), 3.956(3H, s), 6.744(1H, d, J=8.81 Hz), 6.880(2H, d, J=8.81 Hz), 7.122(1H, s), 7.200(2H, d, J=8.81 Hz), 7.48-7.59(4H, m), 8.215(1H, d, J=2.68 Hz), 8.357(1H, dd, J=8.05, 2.68 Hz).

Example 30

3-Carbamoyl-5-(4-methoxyphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 4 using

3-ethoxycarbonyl-5-(4-methoxyphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 27 to give 262mg of desired compound (95.2%).

MP : 103-104°C.

MS : 325(M + 1).

IR (KBr) : 3444.24, 1687.41, 1610.27, 1500.35, 1388.50, 1290.14, 1251.58, 1182.15, 835.03, 786.81.

NMR ($CDCl_3$, δ) : 3.758(3H, s), 3.876(3H, s), 6.908(1H, d, J=8.81 Hz), 6.917(1H, s), 6.941(2H, d, J=8.79 Hz), 7.214(2H, d, J=8.79 Hz), 7.353(1H, br.s), 7.612(1H, br.s), 7.710(1H, dd, J=8.81, 2.74 Hz), 8.160(1H, d, J=2.74 Hz).

Example 31

3-Cyano-5-(4-methoxyphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 5 using 3-carbamoyl-5-(4-methoxyphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 30 to give 40mg of desired compound (21.2%).

MS : 307(M + 1).

IR (NaBr) : 2240.88, 1610.27, 1575.56, 1498.42, 1415.49, 1390.42, 1292.07, 1255.43, 1180.22, 1022.09, 833.098.

NMR ($CDCl_3$, δ) : 3.819(3H, s), 3.952(3H, s), 6.755(1H, d, J=8.97 Hz), 6.837(1H, s), 6.874(2H, d, J=8.89 Hz), 7.128(2H, d, J=8.89 Hz), 7.520(1H, dd, J=8.97, 3.02 Hz), 8.092(1H, d, J=3.02 Hz).

Example 32

3-Carboxy-5-(4-methoxylphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 20

using
3-ethoxycarbonyl-5-(4-methoxyphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 27 to give 1.2 g of desired compound (76.7%).

MP : 144-145°C.
MS : 326(M + H)
IR (KBr) : 1712.48, 1610.27, 1498.42, 1390.42, 1288.22, 1251.58, 1184.08, 1024.02, 831.17, 754.03.
NMR ($CDCl_3$, δ) : 3.815(3H, s), 3.952(3H, s), 6.753(1H, d, J=9.11 Hz), 6.867(2H, d, J=8.87 Hz), 7.041(1H, s), 7.158(2H, d, J=8.87 Hz), 7.588(1H, dd, J=9.11, 2.44 Hz), 8.136(1H, d, J=2.44 Hz).

Example 33
3-(t-Butoxycarbonylamino)-5-(4-methoxylphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 21 using
3-carboxy-5-(4-methoxylphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 32 to give 450 mg of desired compound (73.9%).

MP : 166-167°C.
MS : 419(M + Na).
IR (KBr) : 1724.05, 1610.27, 1575.56, 1535.06, 1496.49, 1384.64, 1286.29, 1247.72, 1162.87.
NMR ($CDCl_3$, δ) : 1.578(9H, s), 3.804(3H, s), 3.926(3H, s), 6.700(1H, d, J=8.95 Hz), 6.723(1H, s), 6.829(2H, d, J=8.91 Hz), 7.163(2H, d, J=8.91 Hz), 7.468(1H, dd, J=8.95, 2.38 Hz), 8.041(1H, d, J=2.38 Hz).

Example 34
3-Amino-5-(4-methoxylphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole hydrochloride

Reaction was carried out in a manner similar to Example 22 using 3-(t-Butoxycarbonylamino)-5-(4-methoxylphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 33 to give 286 mg of desired compound (95.7%). The product was directly used in the next step.

Example 35

3-Chloro-5-(4-methoxylphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole hydrochloride

Reaction was carried out in a manner similar to Example 23 using 3-Amino-5-(4-methoxylphenyl)-1-(6-methoxy-3-pyridyl)-1H-pyrazole hydrochloride obtained by Example 34 to give 100 mg of desired compound (32.8%).

MS : 316(M + 1)

IR (NaBr) : 1610.27, 1496.49, 1384.64, 1292.07, 1253.50, 1176.36, 1024.02, 833.098.

NMR ($CDCl_3$, δ) : 3.807(3H, s), 3.930(3H, s), 6.378(1H, s), 6.866(1H, d, J=8.77 Hz), 6.848(2H, d, J=8.73 Hz), 7.129(2H, d, J=8.73 Hz), 7.523(1H, dd, J=8.77, 2.64 Hz), 8.046(1H, d, J=2.64 Hz).

Example 36

1-(4-Methoxyphenyl)-5-(6-methoxy-3-pyridyl)-3-trifluoromethy 1-1H-pyrazole

A mixture of 2-methoxy-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine obtained by Preparation 3 (1.0 g) and 4-methoxyphenylhydrazine hydrochloride (748 mg) in acetic acid (6 ml) was heated at 60°C for 1.5 hours. After cooling, the reaction mixture was poured onto water and extracted twice with toluene. The organic layer

was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was column chromatographed on silica gel and recrystalized from isopropyl alcohol to give 1.07 g of desired compound (75.7%).

MS : 316(M + 1).
IR (KBr): 1615, 1560, 1515, 1470, 1430,1390.
NMR ($CDCl_3$, δ) : 3.83(3H, s), 3.94(3H, s), 6.65-8.11(8H, m).

Example 37
1-(4-Chlorophenyl)-5-(6-methoxy-3-pyridyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methoxy-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine and 4-chlorophenylhydrazine hydrochloride to give 200 mg of desired compound (34.9%).

MS : 354(M + H).
IR (KBr): 3041, 3019, 3006, 2991, 2950, 1612, 1562, 1498, 1465, 1436, 1394, 1286, 1236, 1155, 1133, 1091, 1018, 968, 833, 730.
NMR ($CDCl_3$, δ) : 3.95(3H, s), 6.69(1H, d, J=8.5Hz), 6.73(1H, s), 7.24-7.40(4H, m), 7.49(1H, s), 8.10(1H, d, J=2.1Hz).

Example 38
1-(4-Cyanophenyl)-5-(6-methoxy-3-pyridyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methoxy-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine and 4-cyanophenylhydrazine hydrochloride to give 200 mg of desired compound (28.7%).

MS : 345(M + H).
IR (KBr): 2952, 1610, 1560, 1504, 1467, 1444, 1423, 1388, 1297,

1286, 1236, 1149, 1137, 1099, 1016, 970, 937, 844, 823, 817.
NMR ($CDCl_3$, δ): 3.96(3H, s), 6.76(1H, d, J=8.3Hz), 6.77(1H, s), 7.35(1H, dd, J=2.583Hz), 7.47(2H, d, J=8.7Hz), 7.69(2H, d, J=8.7Hz), 8.10(1H, d, J=2.5Hz).

Example 39

1-(4-Fluoro-3-methylphenyl)-5-(6-methoxy-3-pyridyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methoxy-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine and 4-Fluoro-3-methylphenylhydrazine hydrochloride to give 200 mg of desired compound (35.2%).

MS : 352(M + H).
IR (neat): 3434, 3403, 2956, 1610, 1562, 1504, 1463, 1423, 1390, 1365, 1286, 1251, 1230, 1162, 1132, 1101, 1024, 977, 815, 757.
NMR ($CDCl_3$, δ): 2.27(3H, d, J=2.1Hz), 3.95(3H, s), 6.67-6.72(2H, m), 7.00(2H, m), 7.30(2H, m), 8.58(1H, d, J=2.5Hz).

Example 40

1-(2,3-Dihydro-5-benzofuranyl)-5-(6-methoxy-3-pyridyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methoxy-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine and 5-(2,3-dihydrobenzofuranyl)hydrazine to give 220.3 mg of desired compound (30.1%).

MS : 362(M + H).
IR (KBr) : 1608, 1548, 1494, 1469, 1430, 1394, 1361, 1295, 1276, 1263, 1238, 1214, 1160, 1122, 1025, 973, 937, 883, 840, 808.
NMR ($CDCl_3$, δ) : 3.21(2H, t, J=8.7Hz), 3.94(3H, s), 4.63(2H, t, J=8.7Hz), 6.66-6.74(3H, m), 6.95(1H, dd, J=2.585Hz), 7.22(1H, br), 7.35(1H, dd, J=2.586Hz), 8.10(1H, d, J=2.5Hz).

Example 41

1-(6-Methoxy-3-pyridyl)-5-(6-methoxy-3-pyridyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methoxy-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine and 6-methoxy-3-pyridylhydrazine hydrochloride to give 450 mg (31.8%) of desired compound.

MS : 351(M + H).
IR (neat) : 3434, 3218, 3052, 3016, 2985, 2952, 1610, 1567, 1498, 1465, 1440, 1392, 1286, 1238, 1162, 1132, 1101, 1022, 973, 831.
NMR ($CDCl_3$, δ) : 3.94(6H, s*2), 6.69-6.80(3H, m), 7.36(1H, dd, J=2.586Hz), 7.58(1H, dd, J=2.889Hz), 8.10(2H, m).

Example 42

5-(6-Methoxy-3-pyridyl)-1-(4-nitrophenyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methoxy-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine and 4-nitrophenylhydrazine hydrochloride to give 600 mg of desired compound (54.3%).

MS : 365(M + H).
IR (KBr) : 3048, 2992, 1610, 1562, 1529, 1469, 1442, 1388, 1351, 1297, 1286, 1272, 1238, 1151, 1103, 1016, 970, 862, 827, 754.
NMR ($CDCl_3$, δ): 3.97(3H, s), 6.75(1H, d, J=8.6Hz), 6.78(1H, s), 7.36(1H, dd, J=2.586Hz), 7.53(2H, d, J=9.1Hz), 8.11(1H, d, J=2.5Hz), 8.26(2H, d, J=9.1Hz).

Example 43

1-(4-Aminophenyl)-5-(6-methoxy-3-pyridyl)-3-trifluoromethyl-1H-pyrazole

Iron (232 mg) and ammonium chloride (35 mg) were added to a solution of 1-(4-nitrophenyl)-5-(6-methoxy-3-pyridyl)-3-trifluoromethyl-1H-pyrazole obtained by Example 42 in ethanol (4 ml) and water(2 ml). This mixture was refluxed for 1h. It was cooled, filtered, washed with ethanol, evaporated in vacuo. The titled compound was afforded in crude solid. This was used without further purification.

MS : 335(M + H).

Example 44

5-(6-Methoxy-3-pyridyl)-1-[(4-(1-1H-pyrrolyl)phenyl]-3-trifluoromethyl-1H-pyrazole

1-(4-Aminophenyl)-5-(6-methoxy-3-pyridyl)-3-trifluoromethyl-1H-pyrazole obtained by Example 43 was dissolved in acetic acid. To this solution, 2,5-dimethoxy tetrahydrofuran was added. Then, the reaction mixture was stirred at 100°C for 2h. It was added to 1N NaOH under ice cooling, extract with ethyl acetate, wash with NaOH, brine, dry over magnesium sulfate, evaporated in vacuum, column hexane/ethyl acetate = 4/1. The titled compound was afforded 65 mg as white powder (24.6%).

MS : 385(M + H).

IR (KBr) : 1610, 1554, 1529, 1473, 1394, 1359, 1328, 1286, 1267, 1230, 1166, 1128, 1101, 1072, 1039, 1020, 970, 838, 796, 727.

NMR ($CDCl_3$, δ) : 3.95(3H, s), 6.37(2H, dd), 6.73-6.77(2H, m, J=2.125Hz), 7.10(2H, d, J=2.1Hz), 7.37-7.44(5H, m), 8.13(1H, d, J=2.1Hz).

Example 45

3-Difluoromethyl-1-(4-methoxyphenyl)-5-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methoxy-5-(4,4-difluoro-3-oxobutanoyl)pyridine obtained by Preparation 4 and 4-methoxyphenylhydrazine hydrochloride to give 316.1 mg of desired compound (23.6%).

MS : 332(M + H).
IR (KBr) : 1610, 1560, 1517, 1506, 1461, 1455, 1361, 1301, 1294, 1257, 1249, 1174, 1168, 1078, 1025, 1020, 973, 838, 836, 802.
NMR ($CDCl_3$, δ) : 3.82(3H, s), 3.93(3H, s), 6.66(2H, d, J=9.1Hz), 6.76(1H, t, J=54.9Hz), 6.90(2H, d, J=9Hz), 7.17-7.35(3H, m), 8.10(1H, d, J=2.4Hz).

Example 46
3-Ethoxycarbonyl-1-(4-methoxyphenyl)-5-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methoxy-5-(3-ethoxycarbonyl-3-oxopropanoyl)pyridine obtained by Preparation 5 and 4-methoxyphenylhydrazine hydrochloride to give 200 mg of desired compound (14.2%).

MS : 354(M + H).
NMR ($CDCl_3$, δ) : 1.42(3H, t, J=7.1Hz), 3.84(3H, s), 3.95(3H, s), 4.45(2H, q, J=7.1Hz), 6.64(1H, d, J=9.2Hz), 6.85(2H, d, J=11Hz), 7.20-7.35(4H, m), 8.09(1H, d, J=2Hz).

Example 47
3-Carbamoyl-1-(4-methoxyphenyl)-5-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 4 using
1-(4-methoxyphenyl)-5-(6-methoxy-3-pyridyl)-3-ethoxycarbonyl-1H-pyrazole obtained by Example 46 to give 233.6 mg of desired

compound (94.3%).

MS : 325(M + H).
NMR ($CDCl_3$, δ): 3.84(3H, s), 3.94(3H, s), 5.43(2H, br), 6.66(1H, d, J=8.2Hz), 6.87-6.93(3H, m), 7.19-7.36(3H, m), 8.08(1H, d, J=2Hz).

Example 48
3-Cyano-1-(4-methoxyphenyl)-5-(6-methoxy-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 5 using 3-carbamoyl-1-(4-methoxyphenyl)-5-(6-methoxy-3-pyridyl)-1H-pyrazole obtained by Example 47 to give 124.5 mg of desired compound (57.7%).

MS : 307(M + H).
IR (KBr) : 2950, 2233, 1610, 1554, 1511, 1490, 1455, 1440, 1403, 1357, 1292, 1251, 1178, 1120, 1070, 1018, 971, 921, 835, 819.
NMR ($CDCl_3$, δ): 3.83(3H, s), 3.94(3H, s), 6.68(1H, d, J=8.5Hz), 6.84-6.92(3H, m), 7.17-7.33(3H, m), 8.07(1H, d, J=2.5Hz).

Example 49
1-(2,3-Dihydro-5-benzofuranyl)-5-(6-methyl-3-pyridyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methyl-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine obtained by Preparation 6 and 5-(2,3-dihydrobenzofuranyl)hydrazine to give 26 mg of desired compound (29%).

MP : 142-143℃.
Mass : 346(M + 1)

IR (KBr) : 3215, 3124, 3060, 2966, 2918, 1651, 1612.
NMR (DMSO, δ) : 2.46(3H, s), 3.20(2H, t, J=8.8Hz), 4.61(2H, t, J=8.8Hz), 6.79(1H, d, J=8.4Hz), 7.03(1H, dd, J=8.4Hz, 2.3Hz), 7.26(2H, d, J=7.2Hz), 7.33(1H, d, J=2.1Hz), 7.53(1H, dd, J=8.1Hz, 2.3Hz), 8.40(1H, d, J=1.8Hz).

Example 50
1-(4-chrolophenyl)-5-(6-methyl-3-pyridyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methyl-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine obtained by Preparation 6 and 4-chrolophenylhydrazine hydrochloride to give 90 mg of desired compound (41.1%).

MP : 107-108℃.
MS : 338, 340 (M + 1)
IR (KBr) : 3489, 3464, 3435, 3402, 3028, 2981, 1603.
NMR (DMSO, δ) : 2.47(3H, s), 7.28(2H, d, J=8.4Hz), 7.38-7.46(2H, m), 7.52-7.60(3H, m), 8.41(1H, d, J=1.9Hz).

Example 51
1-(4-Fluoro-3-methylphenyl)-5-(6-methyl-3-pyridyl)-3-trifluoromethyl-1H-pyrazole hydrochloride

Reaction was carried out in a manner similar to Example 36 using 2-methyl-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine obtained by Preparation 6 and 4-methoxyphenylhydrazine hydrochloride to give 40 mg of desired compound (27.6%).

MP : 173-176℃.
MS : 336(M + 1).
IR (KBr) : 3435, 3406, 3103, 3033, 2650, 2580, 1645, 1608.
NMR (DMSO, δ) : 2.26(3H, s), 2.56(3H, s), 7.21-7.25(2H, m), 7.29(1H, s), 7.45-7.50(2H, m), 7.74(1H, d, J=8.3Hz), 8.55 (1H, s).

Example 52

3-Ethoxycarbonyl-1-(4-methoxyphenyl)-5-(6-methyl-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-methyl-5-(3-ethoxycarbonyl-3-oxopropanoyl)pyridine obtained by Preparation 7 and 4-methoxyphenylhydrazine hydrochloride to give 0.63 g of desired compound (133.1%).

MS : 338(M + 1).
IR (neat) : 3429, 3406, 2962, 2924, 2858, 1666.
NMR (DMSO, δ) : 1.32(3H, t, J=7.1Hz), 2.45(3H, s), 3.80(3H, s), 4.33(2H, q, J=7.1Hz), 6.99-7.03(2H, m), 7.19-7.31(4H, m), 7.50(1H, dd, J=8.0Hz, 2.4Hz), 8.35(1H, d, J2.0Hz).

Example 53

3-Carbamoyl-1-(4-methoxyphenyl)-5-(6-methyl-3-pyridyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 4 using 1-(4-methoxyphenyl)-5-(6-methyl-3-pyridyl)-3-ethoxycarbonyl-1H-pyrazole obtained by Example 52 to give 0.32 g of desired compound (55.6%).

MP : 135℃ (decomposed).
MS : 309(M + 1).
IR (KBr) : 3433, 3294, 3167, 3012, 2970, 1685, 1608.
NMR (DMSO, δ) : 2.45(3H, s), 3.78(3H, s), 6.98-7.05(3H, m), 7.22-7.35(4H, m), 7.50(1H, dd, J=8.0Hz, 2.3Hz), 7.61-7.66(1H, m), 8.34(1H, d, J=2.2Hz).

Example 54

3-Cyano-1-(4-methoxyphenyl)-5-(6-methyl-3-pyridyl)-1H-pyrazo

le hydrochloride

3-Carbamoyl-1-(4-methoxyphenyl)-5-(6-methyl-3-pyridyl)-1H-pyrazole obtained by Example 53 (250 mg) and $POCl_3$ (227 ml) in N,N-Dimethylformamide (3 ml) were stirred at room temperature for 1 hour. The reaction mixture was poured into sodium bicarbonate aq., and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, and evaporated in vacuo. The residue was dissolved in ethyl acetate. Then 4N hydrochloric acid in ethyl acetate was added. Resulting precipitates were corrected by filtration to give 110 mg of desired compound (41.5%).

MP :125-128℃.

MS : 291(M + 1) (free).

IR (KBr) : 3429, 3400, 3120, 3076, 2968, 2906, 2835, 2652, 2243, 1643, 1608.

NMR (DMSO, δ) : 2.58(3H, s), 3.08(3H, s), 7.03(2H, dd, J=8.7Hz, 2.0Hz), 7.36 (2H, dt, J=9.7Hz, 2.9Hz), 7.53 (1H, s), 7.55(1H, s), 7.77(1H, dd, J=8.2Hz, 2.2Hz), 8.53(1H, d, J=2.0Hz).

Example 55

5-(6-Chloro-3-pyridyl)-3-difluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole

Reaction was carried out in a manner similar to Example 36 using 2-chloro-5-(4,4-difluoro-3-oxobutanoyl)pyridine obtained by Preparation 8 and 4-methoxyphenylhydrazine hydrochloride to give 0.79 g of desired compound (61.1%).

MS : 336(M + 1).

IR (neat) : 3454, 3361, 3130, 3064, 3005, 2962, 2841, 1601.

NMR (DMSO, δ) : 3.80(3H, s), 3.87(1H, d, J=9.9Hz), 4.82(1H, s), 6.99-7.03(2H, m), 7.30(2H, dd, J=6.8Hz, 2.1Hz), 7.54(1H, d, J=8.5Hz), 7.67(1H, dd, J=8.3Hz, 2.5Hz), 8.36(1H, d, J=2.2Hz).

Example 56

3-Difluoromethyl-1-(4-methoxyphenyl)-5-(6-methyl-3-pyridyl)-1H-pyrazole hydrochloride

5-(6-Chloro-3-pyridyl)-3-difluoromethyl-1-(4-methoxyphenyl)-1H-pyrazole obtained by Example 55 (0.4 g), 2N methylzincchloride in tetrahydrofuran (3.57 ml) and $Pd(PPh_3)_4$ (42 mg) were stirred at reflux condition for 1 hour. After the reaction mixture was quenched with dil. hydrochloric acid, extracted with ethyl acetate, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with n-hexane-ethyl acetate (2:1) and evaporated in vacuo. The residue was dissolved in ethyl acetate and 4N hydrochloric acid / ethyl acetate was added. Resulting precipitates were collected by filtration to give 0.3 g of desired compound (71.6%).

MP : 170-173℃.

MS : 316(M + 1) (free).

IR (KBr) : 3433, 3105, 3064, 3022, 2966, 2902, 2839, 2555, 2484, 2426, 2040, 1643, 1604.

NMR (DMSO, δ) : 2.64(3H, s), 3.78(1H, d, J=7.1Hz), 3.80(3H, s), 6.99-7.05(2H, m), 7.13-7.18(1H, m), 7.33(2H, dd, J=9.7Hz, 2.9Hz), 7.64(1H, d, J=8.3Hz), 7.91(1H, dd, J=8.2Hz, 2.1Hz), 8.62(1H, d, =2.0Hz).

Example 57

3-(6-Chloro-3-pyridyl)-2-(4-nitrophenyl)-5-trifluoromethyl-3,4-dihydro-2H-pyrazol-3-ol

2-chloro-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine obtained by Preparation 9 (3.3 g) and 4-nitrophenylhydrazine (4.02 g) in acetic acid (3 ml) was stirred at room temperature for overnight. The reaction mixture was poured into a mixture of ethyl acetate and water. The organic layer was dried over

magnesium sulfate and evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with n-hexane-ethyl acetate (2:1) to give 1.54 g of desired compound. (30.4%)

MP : 249-251℃.

MS : 387(M + 1).

IR (KBr) : 3099, 3074, 2972, 2898, 2710, 2661.

NMR (DMSO, δ) : 3.68-3.78(1H, m), 4.11-4.21(1H, m), 7.64-7.73(3H, m), 8.17-8.25(2H, m), 8.31(1H, dd, J=8.3Hz, 2.5Hz), 8.82(1H, d, J=1.9Hz), 8.92 1H, s).

Example 58

2-(4-Aminophenyl)-3-(6-chloro-3-pyridyl)-5-trifluoromethyl-3,4-dihydro-2H-pyrazol-3-ol

3-(6-Chloro-3-pyridyl)-2-(4-nitrophenyl)-5-trifluoromethyl-3,4-dihydro-2H-pyrazol-3-ol obtained by Example 57 (0.8 g), Fe (0.8 g) and NH_4Cl (80 mg) were stirred at reflux condition for 2 hours. After cooling room temperature, the reaction mixture was filtrated. And the filtrate was evaporated. The residue was poured into a mixture of ethyl acetate and water. The organic layer was dried over magnesium sulfate and evaporated in vacuo. Resulting precipitates were collected by filtration to give 0.59 g of desired compound (79.9%).

MP : 159-161℃.

MS : 357(M + 1).

IR (KBr) : 3467, 3373, 3211, 3093, 3051, 2976, 1626.

NMR (DMSO, δ) : 3.43-3.53(1H, m), 3.57-3.68(1H, m), 5.01(2H, s), 6.51(2H, d, J=8.7 Hz), 6.99(2H, d, J=8.5Hz), 7.55(1H, d, J=8.4Hz), 7.77(1H, s), 8.10(1H, dd, J=8.3Hz, 2.4Hz), 8.64 (1H, d, J=2.2Hz).

Example 59

2-(4-Aminophenyl)-3-(6-methyl-3-pyridyl)-5-trifluoromethyl-3

,4-dihydro-2H-pyrazol-3-ol

2-(4-Aminophenyl)-3-(6-chloro-3-pyridyl)-5-trifluoromethyl-3,4-dihydro-2H-pyrazol-3-ol obtained by Example 58 (0.5 g), 2N methylzincchloride in tetrahydrofuran (4.2 ml) and $Pd(PPh_3)_4$ (49 mg) were stirred at reflux condition for 1 hour. After the reaction mixture was quenched with dil hydrochloric acid, extracted with ethyl acetate, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with n-hexane-ethyl acetate (2:1) to give 0.24 g of desired compound (50.9%).

MP : 125-128℃.
MS : 337(M + 1).
IR (KBr) : 3454, 3357, 3219, 3039, 2972, 2700, 1624.
NMR (DMSO, δ) : 2.55(3H, s), 3.47-3.50(1H, m), 3.65-3.74(1H, m), 4.98(2H, s), 6.51(2H, d, J=8.6Hz), 6.98(2H, d, J=8.6Hz), 7.27-7.34(1H, m), 7.67(1H, s), 7.93(1H, dd, J=8.1Hz, 2.2Hz), 8.69 (1H, d, J=2.0Hz).

Example 60
5-(6-Methyl-3-pyridyl)-1-[4-(1-pyrrolyl)phenyl]-3-trifluoromethyl-1H-pyrazole

2-(4-Aminophenyl)-3-(6-methyl-3-pyridyl)-5-trifluoromethyl-3,4-dihydro-2H-pyrazol-3-ol obtained by Example 59 (0.2 g) and 2,5-dimethoxytetrahydrofuran (116 ml) in acetic acid (2 ml) were stirred at 100℃ for 1 hour. After cooling to room temperature, the reaction mixture was poured into sodium bicarbonate aq., and extracted with ethyl acetate. The organic layer was washed with aq. sodium bicarbonate, water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with n-hexane-ethyl acetate (2:1) to give 52 mg of desired compound

(23.7%).

MP : 190-191℃.

MS : 369(M + 1).

IR (KBr) : 3431, 3404, 3124, 3074, 2964, 1608.

NMR ($CDCl_3$, δ) : 2.61(3H, s), 6.40(2H, t, J=2.1Hz), 7.15(2H, t, J=2.1Hz), 7.21-7.26(1H, m), 7.50-7.70(4H, m), 8.06(1H, dd, J=8.1Hz, 2.3Hz), 8.95(1H, d, J=2.2Hz).

Example 61

5-(4-Methoxyphenyl)-1-(6-methyl-3-pyridyl)-3-trifluoromethyl-1H-pyrazole hydrochloride

A mixture of 1-(6-chloro-3-pyridyl)-5-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole obtained by Example 25 (1.0g) and CuBr(811mg) in tetrahydrofuran (10ml) was cooled at -78℃. Methyl magnesium bromide (1N tetrahydrofuran solution 8eq. 5.6ml) was added to above solution and stirred for 20min. I was added to the reaction mixture and then warmed to 80℃ (14:00-16:00). The reaction mixture was quenched with sat. NH_4Cl and then filtered on celite. The crust was washed with ethyl acetate-water. The organic layer was washed with brine and dried. After removal of the solvent, the residue was purified with column chromato (Silica / 20% ethyl acetate - toluene). Hydrochloric acid - ethyl acetate was added to the obtained oil and triturated with diethylether to afford 300 mg of desired compound (63.7%).

MP : 124-124℃.

MS : 334(M + 1, free).

NMR (DMSO, δ) : 2.61(3H, s), 3.77(3H, s), 7.13(1H, s), 6.90-7.30(4H, m), 7.59(1H, d, J=8Hz), 7.93(1H, d, J=8,2Hz), 8.59(1H, d, J=2Hz).

Example 62

5-(4-Methoxyphenyl)-1-(6-methyl-3-pyridyl)-3-trifluoromethyl

-1H-pyrazole

Reaction was carried out in a manner similar to Example 27 using 4-methoxy-1-(4,4,4-trifluoro-3-oxobutanoyl)benzene and 4-methylphenylhydrazine hydrochloride obtained by Preparation 12 to give 175.4 mg of desired compound (35.1%).

MS : 334(M + H).
IR (KBr) : 1610, 1581, 1571, 1498, 1467, 1446, 1240, 1162, 1132, 1101, 1033, 973, 833, 806.
NMR ($CDCl_3$, δ) : 2.58(3H, s), 3.84(3H, s), 6.70(1H, s), 6.86(2H, d, J=8.8Hz), 7.10-7.20(3H, m), 7.59(1H, dd, J=2.583Hz), 8.41(1H, d, J=2.5Hz).

Example 63
5-(4-Cyanophenyl)-1-(6-methyl-3-pyridyl)-3-trifluoromethyl-1 H-pyrazole

Reaction was carried out in a manner similar to Example 27 using 4-cyano-1-(4,4,4-trifluoro-3-oxobutanoyl)benzene and 5-hydrazino-2-methylpyridine hydrochloride to give 125 mg of desired compound (18.4%).

MS : 329(M + H).
IR (KBr) : 2221, 1604, 1481, 1444, 1394, 1274, 1238, 1155, 1132, 1095, 1031, 970, 925, 844, 809, 732, 723.
NMR ($CDCl_3$, δ) : 2.61(3H, s), 6.85(1H, s), 7.23(1H, d, J=9.1Hz), 7.35(2H, d, J=8.2Hz), 7.58(1H, dd, J=2.191Hz), 7.66(2H, d, J=8.2Hz), 8.38(1H, d, J=2.1Hz).

Example 64
5-(4-Methylphenyl)-1-(6-methyl-3-pyridyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 27

using 4-methyl-1-(4,4,4-trifluoro-3-oxobutanoyl)benzene and 5-hydrazino-2-methylpyridine hydrochloride to give 210 mg of desired compound (30.5%).

MS : 318(M + H).
IR (KBr) : 3060, 3025, 2921, 1604, 1482, 1473, 1448, 1384, 1278, 1236, 1139, 1099, 1051, 1033, 973, 846, 835, 821, 792, 734.
NMR ($CDCl_3$, δ): 2.35(3H, s), 2.58(3H, s), 6.73(1H, s), 7.07-7.20(5H, m), 7.60(1H, dd, J=2.583Hz), 8.40(1H, d, J=2.5Hz).

Example 65
5-(4-Methoxyphenyl)-1-[6-(1-1H-pyrrolyl)-3-pyridyl]-3-trifluoromethyl-1H-pyrazole

Pyrrol was added to 1-(6-Chloro-3-pyridyl)-5-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole obtained by Example 25 in N,N-Dimethylformamide at room temperature and stirred at 80℃ on an oil bath for 5 hours, 100℃ for 3 hours. Another NaH (4 eq) was added at room temp., stirred at 100℃. 5 Hours after, poured into water, partitioned between ethyl acetate and sat. aq. NH_4Cl 3.6% aq. hydrochloric acid, sat. aq. sodium bicarbonate, sat. aq. NaCl, dried over magnesium sulfate, concentrated in vacuo, and purified by prep TLC.

MS : 385(M + H).
IR (KBr) : 3124, 1608, 1585, 1490, 1450, 1402, 1336, 1229, 1263, 1234, 1182, 1153, 1126, 1066, 1024, 970, 925, 825, 808, 736.
NMR ($CDCl_3$, δ) : 3.82(3H, s), 6.37(2H, d, J=4.5Hz), 6.72(1H, s), 6.89(2H, d, J=8.7Hz), 7.19(2H, d, J=8.7Hz), 7.31(1H, d, J=8.5Hz), 7.48(2H, d, J=4.5Hz), 7.75(1H, dd, J=2.085Hz), 8.33(1H, d, J=2Hz).

Example 66
5-(4-Methoxyphenyl)-1-[6-(1-1H-pyrazolyl)-3-pyridyl]-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 65 using
1-(6-chloro-3-pyridyl)-5-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole obtained by Example 25 and pyrazole to give 35 mg of desired compound (64.3%).

MS : 386(M + H).
IR (KBr) : 3127, 2969, 1608, 1517, 1484, 1444, 1390, 1301, 1261, 1236, 1186, 1151, 1126, 1099, 1031, 970, 929, 842, 809, 763.
NMR ($CDCl_3$, δ): 3.82(3H, s), 6.48(1H, d, J=4.1Hz), 6.73(1H, s), 6.90(2H, d, J=8.7Hz), 7.16(2H, d, J=8.7Hz), 7.40(2H, m), 8.00(1H, d, J=8.4Hz), 8.35(1H, d, J=2.4Hz), 8.52(1H, d, J=2.4Hz).

Example 67
1-[6-(1-1H-Imidazolyl)-3-pyridyl]-5-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazole

Reaction was carried out in a manner similar to Example 65 using
1-(6-chloro-3-pyridyl)-5-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole obtained by Example 25 and imidazole to give 40 mg of desired compound (73.4%).

MS : 386(M + H).
IR (neat) : 2962, 1610, 1488, 1409, 1303, 1240, 1157, 1132, 1099, 1056, 971, 831, 808.
NMR ($CDCl_3$, δ) : 3.83(3H, s), 6.74(1H, s), 6.91(2H, d, J=8.2Hz), 7.18(3H, m), 7.37(1H, d, J=8Hz), 7.63(1H, s), 7.84(1H, dd, J=8.02Hz), 8.33(1H, s), 8.41(1H, d, J=2Hz).

Preparation 1
5-Hydrazino-2-methoxypyridine hydrochloride

To a solution of 2.48g of 5-amino-2-methoxy-pyridine in 40ml

1N hydrochloric acid at 5°C, was added 1.65g of sodium nitrite in 12ml of water and stirred 30 min. at 5°C, then added 16.2g of tin (II) chloride dehydrate, stirred for 30 min. and evaporated under reduced pressure to give crude desired compound. This product was allowed to use directly in the next step.

Preparation 2
5-Acetyl-2-methoxypyridine

A mixture of 5-acetyl-2-chloropyridine (7.8 g) and 28% sodium methoxide (3.25g) in methanol (50 ml) was refluxed for 1.5 h. The reaction mixture was filtrate on celite, and evaporated reduced pressure. The residue was dissolved in ethyl acetate, washed with brine, and dried over magnesium sulfate. After removal of the solvent, 6.7 g (88.4%) of desired compound was obtained.

IR (KBr) : 1675, 1600, 1565, 1495, 1460.
NMR ($CDCl_3$, δ) : 2.57(3H, s), 4.01(3H, s), 6.77-8.79(3H, m).

Preparation 3
2-Methoxy-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine

To a suspension of sodium methoxide (3.0 g) in N,N-Dimethylformamide (5.4ml) was added dropwise 5-acetyl-2-methoxypyridine obtained by Preparation 2 (6.0g) in N,N-Dimethylformamide (13ml) under ice-NaCl-cooling (5°C) over 10min. After stirring for 15min, ethyl trifluoroacetate (6.77g) in N,N-Dimethylformamide (1.3ml) was added dropwise over 20min at the same temperature. After stirring for 1 hour, the reaction mixture was quenched with ice-water and adjusted to pH 4.0 with 10% aqueous hydrochloric acid. After stirring 20min, the precipitate was filtered, washed with water and dried to give 9.0g of desired compound (91.7%).

IR (KBr) : 3430, 1665, 1610, 1565, 1505.

MS : 246(M - 1).

NMR($CDCl_3$, δ) : 4.04(3H, s), 5.03(2H, s), 6.81-8.82(3H, m).

Preparation 4

2-Methoxy-5-(4,4-difluoro-3-oxobutanoyl)pyridine

Reaction was carried out in a manner similar to Preparation 3 using 5-acetyl-2-methoxypyridine obtained by Preparation 2 and ethyl difluoroacetate to give desired compound.

Preparation 5

2-Methoxy-5-(3-ethoxycarbonyl-3-oxopropianoyl)pyridine

Reaction was carried out in a manner similar to Preparation 3 using 5-acetyl-2-methoxypyridine obtained by Preparation 2 and diethyl oxalate to give desired compound.

Preparation 6

2-Methyl-5-(4,4,4-trifluoro-3-oxobutanioyl)pyridine

1-(6-Methyl-3-pyridyl)ethan-1-one (0.18 g) and ethyl trifluoroacetate (0.19 ml) was dissolved in N,N-dimethylformamide (2 ml). After NaH (61 mg) was added, the reaction mixture was stirred at room temperature for 1 hour. The mixture was poured into ice dil. hydrochloric acid aq. (pH 6). Then extracted with ethyl acetate. The organic layer was washed with sat. sodium bicarbonate and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with n-hexane-ethyl acetate (2:1) to give 83 mg of desired compound (27.0%).

MP : 255℃ (decomposed).

MS : 230(M - 1)

IR (KBr) : 3261, 3255, 3170, 3124, 3072, 3024, 2964, 1635, 1601.

NMR ($CDCl_3$, δ) : 2.68(3H, s), 6.56(1H, s), 7.33(1H, d, J=8.2Hz),

8.12(1H, dd, J=8.2Hz, 2.1Hz), 9.05(1H, d, J=2.1Hz).

Preparation 7

2-Methyl-5-(3-ethoxycarbonyl-3-oxopropanoyl)pyridine

Reaction was carried out in a manner similar to Preparation 3 using 5-acetyl-2-methylpyridine and diethyl oxalate to give 0.17 g of desired compound (32.6%).

MP : 74-76℃.

MS : 236(M + 1).

IR (KBr) : 3093, 2989, 2962, 1734, 1674, 1601.

NMR (DMSO, δ) : 1.32(3H, t, J=7.1H), 2.58(3H, s), 3.87(1H, s), 4.32(2H, q, J=7.1Hz), 7.13(1H, s), 7.47(1H, d, J=8.2Hz), 8.32(1H, dd, J=8.2Hz, 2.4Hz), 9.10(1H, d, J=2.1Hz).

Preparation 8

2-Chloro-5-(4,4-difluoro-3-oxobutanoyl)pyridine

Reaction was carried out in a manner similar to Preparation 3 using 5-acetyl-2-chloropyridine and ethyl difluoroacetate to give 0.93 g of desired compound (82.6%).

MS : 234(M + 1).

IR (neat) : 3440, 3429, 3379, 2960, 1724, 1664, 1628.

NMR (DMSO, δ) : 3.90(1H, s), 4.00(1H, s), 6.93(1H, s), 7.73(1H, d, J=8.1Hz), 8.30-8.36(1H, m), 9.06(1H, d, J=2.5Hz).

Preparation 9

2-Chloro-5-(4,4,4-trifluoro-3-oxobutanoyl)pyridine

Reaction was carried out in a manner similar to Preparation 3 using 5-acetyl-2-chloropyridine and ethyl trifluoroacetate to give 3.85 g of desired compound (82.1%).

IR (neat) : 3101, 2956, 1732, 1666, 1657, 1635, 1628.
NMR (DMSO, δ) : 3.97(1H, s), 6.88(1H, s), 7.73(1H, d, J=8.6 Hz), 8.42(1H, dd, J=8.5Hz, 2.6Hz), 9.04(1H, d, J=2.4Hz).

Preparation 10
tert-Butyl 6-methyl-3-pyridylcarbamate

Reaction was carried out in a manner similar to Example 21 using 5-carboxy-2-methylpyridine to give 5.15 g of desired compound (89.2%).

MS : 231(M + Na).
NMR ($CDCl_3$, δ) : 1.52(9H, s), 2.50(3H, s), 6.51(1H, br), 7.08(1H, d, J=8.4Hz), 7.86(1H, dd, J=2.684Hz), 8.31(1H, d, J=2.6Hz).

Preparation 11
6-Methyl-3-pyridinamine dihydrochloride

Reaction was carried out in a manner similar to Example 22 using tert-Butyl 6-methyl-3-pyridylcarbamate obtained by Preparation 10 to give 2.3 g of desired compound (88.6%).

MS : 131(M + Na).

Preparation 12
5-Hydrazino-2-methylpyridine

Reaction was carried out in a manner similar to Preparation 1 using 6-Methyl-3-pyridinamine dihydrochloride obtained by Preparation 11 to give desired compound.

MS : 182(M + H, free).

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the compounds (I) are shown

in the following.

[A] ANALGESIC ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Analgesic activity of a single dose of agents in arthritic rats was studied.

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50 μl of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22.

Drugs (Test compounds) were administered and the pain threshold was measured 2hr after drug administration. The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co.Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

Test compound (Example No.)	Dose (mg/kg)	The coefficient of analgesic
1	3.2	1.66
2	3.2	1.63
5	3.2	1.59
15	3.2	1.54
19	3.2	1.63
36	3.2	1.75

[B] Inhibiting activity against COX-I and COX-II (Whole Blood Assay):

(i) Test Method :

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500μl aliquots of human whole blood were immediately incubated with 2μl of either dimethyl sulfoxide vehicle or a test compound at final concentrations for 1hr at 37℃ to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5μl of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4℃ to obtain serum. A 100 μl aliquot of serum was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4℃ and was assayed for TXB_2 using an enzyme immunoassay kit according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of thromboxane B_2(TXB_2) production relative to control incubations containing dimethyl sulfoxide vehicle.

The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500μl aliquots of human whole blood were incubated with either 2μl dimethyl sulfoxide vehicle or 2μl of a test compound at final

concentrations for 15 min at 37 ℃. This was followed by incubation of the blood with 10 μl of 5mg/ml lipopolysaccharide for 24hr at 37℃ for induction of COX-II. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000 x g for 5 min at 4 ℃ to obtain plasma. A 100 μl aliquot of plasma was mixed with 400 μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4℃ and was assayed for prostaglandin E_2 (PGE_2) using a radioimmunoassay kit after conversion of PGE_2 to its methyl oximate derivative according to the manufacturer's procedure.

For a test compound, the results were expressed as percent inhibition of PGE_2 production relative to control incubations containing dimethyl sulfoxide vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
1	< 0.01	≧ 0.1
2	< 0.01	≧ 0.1
5	< 0.01	≧ 0.1
9	< 0.01	≧ 0.1
14	< 0.01	≧ 0.1
15	< 0.01	≧ 0.1
19	< 0.01	≧ 0.1
23	< 0.01	≧ 0.1
29	< 0.01	≧ 0.1

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the

present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc. So compound (I) or a salt thereof is expected to be useful as medicament.

The object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.], inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, particularly those in which

lipoxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

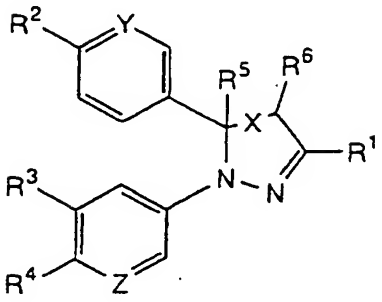
Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

And compound (I) or a salt thereof is expected to be useful as analgesic agent, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, or juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury without causing gastrointestinal disorders.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



(I)

wherein

R^1 is halogen, cyano, (lower alkyl)carbonyl, arylcarbonyl, lower alkyl, lower alkyl which is substituted with halogen, lower alkyl which is substituted with hydroxy, carboxy, (lower alkoxy)carbonyl, carbamoyl, N-(lower alkyl)carbamoyl, amino, or (lower alkoxy)carbonylamino;

R^2 is halogen, cyano, lower alkyl, lower alkoxy, carboxy, (lower alkoxy)carbonyl, or carbamoyl;

R^3 is hydrogen or lower alkyl;

R^4 is halogen, cyano, nitro, lower alkyl, lower alkoxy, amino, or heteroaryl containing nitrogen atom(s);

R^3 and R^4 may form 2,3-dihydrofuryl;

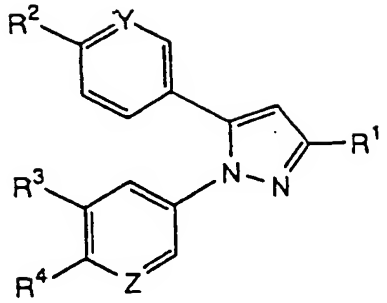
X is single or double bond between two carbon atoms;

R^5 is hydroxy and R^6 is hydrogen in case that X is single bond, or R^5 and R^6 do not exist in case that X is double bond;

Y is CH and Z is N, Y is N and Z is CH, or Y is N and Z is N;

or pharmaceutically acceptable salts thereof.

2. A compound of the formula (II):



(II)

wherein

R^1 is halogen, cyano, (lower alkyl)carbonyl, arylcarbonyl, lower alkyl, lower alkyl which is substituted with halogen, lower alkyl which is substituted with hydroxy, carboxy, (lower alkoxy)carbonyl, carbamoyl, N-(lower alkyl)carbamoyl, amino, or (lower alkoxy)carbonylamino;

R^2 is halogen, cyano, lower alkyl, lower alkoxy, carboxy, (lower alkoxy)carbonyl, or carbamoyl;

R^3 is hydrogen or lower alkyl;

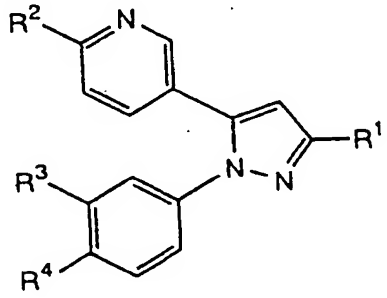
R^4 is halogen, cyano, nitro, lower alkyl, lower alkoxy, amino, or heteroaryl containing nitrogen atom(s);

R^3 and R^4 may form 2,3-dihydrofuryl;

Y is CH and Z is N, Y is N and Z is CH, or Y is N and Z is N;

or pharmaceutically acceptable salts thereof.

3. A compound of the formula (III):



(III)

wherein

R^1 is halogen, cyano, (lower alkyl)carbonyl, arylcarbonyl, lower alkyl, lower alkyl which is substituted with

halogen, lower alkyl which is substituted with hydroxy, carboxy, (lower alkoxy)carbonyl, carbamoyl, N-(lower alkyl)carbamoyl, amino, or (lower alkoxy)carbonylamino;

R^2 is halogen, cyano, lower alkyl, lower alkoxy, carboxy, (lower alkoxy)carbonyl, or carbamoyl;

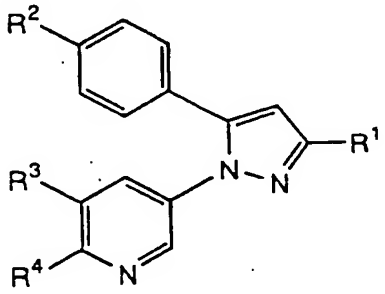
R^3 is hydrogen or lower alkyl;

R^4 is halogen, cyano, nitro, lower alkyl, lower alkoxy, amino, or heteroaryl containing nitrogen atom(s);

R^3 and R^4 may form 2,3-dihydrofuryl;

or pharmaceutically acceptable salts thereof.

4. A compound of the formula (IV):



(IV)

wherein

R^1 is halogen, cyano, (lower alkyl)carbonyl, arylcarbonyl, lower alkyl, lower alkyl which is substituted with halogen, lower alkyl which is substituted with hydroxy, carboxy, (lower alkoxy)carbonyl, carbamoyl, N-(lower alkyl)carbamoyl, amino, or (lower alkoxy)carbonylamino;

R^2 is halogen, cyano, lower alkyl, lower alkoxy, carboxy, (lower alkoxy)carbonyl, or carbamoyl;

R^3 is hydrogen or lower alkyl;

R^4 is halogen, cyano, nitro, lower alkyl, lower alkoxy, amino, or heteroaryl containing nitrogen atom(s);

R^3 and R^4 may form 2,3-dihydrofuryl;

or pharmaceutically acceptable salts thereof.

5. The compound or pharmaceutically acceptable salts thereof

according to any one of Claims 1 to 4, wherein

R^1 is halogen, cyano, arylcarbonyl, or lower alkyl which is substituted with halogen;

R^2 is cyano, lower alkyl, or lower alkoxy;

R^3 is hydrogen;

R^4 is lower alkoxy.

6. A medicament comprising a compound of any one of Claim 1 to 5 as an active ingredient.

7. A pharmaceutical composition comprising a compound of any one of Claim 1 to 5, as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient.

8. A method for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegerative diseases which comprises administering an effective amount of the compound of any one of Claim 1 to 5 to human beings or animals.

9. Use of the compound of any one of Claim 1 to 5 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegerative diseases in human beings or animals.

10. The analgesic agent comprising the compound of any one of Claim 1 to 5, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations without causing gastrointestinal disorders.

11. The analgesic agent of Claim 10, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, or juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis;

pain and tumescence after operation or injury without causing gastrointestinal disorders.

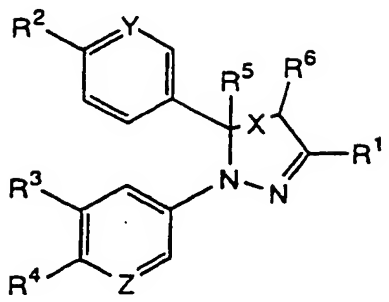
DATED this 6th day of February 2004

Fujisawa Pharmaceutical Co., Ltd.

By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

A B S T R A C T

A compound of the formula (I):



(I)

wherein

R^1 is halogen, etc;

R^2 is lower alkoxy, etc;

R^3 is hydrogen, etc;

R^4 is halogen, etc;

X is single or double bond between two carbon atoms;

R^5 is hydroxy and R^6 is hydrogen, or R^5 and R^6 do not exist;

Y is CH and Z is N, etc;

or pharmaceutically acceptable salts thereof, which are useful as a medicament.